

## REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

### **Status of the Claims**

Claims 3-8, 12, 16 and 20-30 are currently pending in the application. Claims 3-7 are presently withdrawn and claims 8, 12, 16 and 20-30 are presently under examination.

A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

### **Rejection Under 35 U.S.C. § 103(a)**

The Examiner rejects claims 8, 12, 16 and 20-30 as allegedly being obvious over EP 0115627 (“APC”), U.S. Pat. No. 5,759,565 (“Azria”) and U.S. Pat. No. 5,026,825 (“Grebrow”). Applicants respectfully traverse this ground of rejection. Applicants maintain that Azria teaches away from the claimed invention, thus the Examiner relies upon impermissible hindsight reasoning to support his rejection.

In this Office Action, the Examiner concedes that “Azria teaches that concentration[s] of chlorobutanol above 0.6% have undesired effects.” Office Action at 4. That notwithstanding, the Examiner asserts that it would have been obvious to use chlorobutanol as a preservative at “%w/v concentrations below that of 0.6% to prevent any deleterious effects in the composition.” Office Action at 5. The Examiner goes on to state that APC teaches the use of chlorobutanol in the range of 0.001-2.0% w/v and that Grebrow teaches the use of chlorobutanol in ranges from “0.5-1.0 and in Example 9, teaches Chlorobutanol at 0.1% w/v.” Office Action at 4 and 5. Thus, the Examiner concludes that APC and Grebrow “teach a specific example where chlorobutanol is used at much lower concentrations as a preservative....” Office Action at 8.

The Examiner also alleges that “it is clear from Azria et al that chlorobutanol has a deleterious effect at 0.6% and higher, but there is no indication that this would be true for concentrations lower than [sic] the 0.6% that Azria et al teaches....” Office Action at 8.

Applicants reiterate Azria discloses that at concentrations of 0.6%, chlorobutanol was ineffective as a preservative. Specifically, “chlorobutanol at 0.6% in calcitonin nasal pharmaceutical compositions showed insufficient activity against the test fungus *Pen. steckii*...” Azria, col. 2, lines 39-41. The Examiner dismisses this point by stating that “[j]ust because one reference teaches an ingredient to have deleterious properties at a particular concentration...it is not an explicit teaching away from its use at lower concentrations.” Office Action at 8.

What the Examiner fails to acknowledge, however, is that Azria discloses the failure of chlorobutanol to act as a preservative at 0.6%, not just any property of the compound. One of skill in the art reading Azria would have concluded that chlorobutanol did not work as a preservative at concentrations lower than 0.6% because it was ineffective as a preservative at concentrations of 0.6%. This point was also stated in the Declaration of Henry R. Costantino dated August 24, 2007 at page 3, ¶9, ¶10. In other words, Azria taught those skilled in the art that chlorobutanol was ineffective as a preservative at concentrations of 0.6% or less. As such, this disclosure taught away from using 0.6% or less of chlorobutanol—Azria taught that such an amount rendered this preservative ineffective for its intended purpose.

Chlorobutanol is disclosed in both APC and Grebow as one of several preservatives for use in calcitonin formulations, e.g., thimerosol (0.001 – 0.01 w/v%), chlorobutanol (0.5 – 1.0 w/v%) and phenethyl alcohol (0.25 – 0.75 w/v%). *See* APC, page 3, lines 40-55 (describing seven different preservatives); Grebow, col. 12, lines 1-13 (describing nine different preservatives). When trying to capture all possible preservatives generally, both references refer to a broad range of 0.001 – 2.0% w/v for possible preservative concentrations. Regarding chlorobutanol in particular, however, APC and Grebow taught the use of this composition as a preservative, but at a concentration of 0.5 – 1.0 w/v%, *i.e.*, higher than the range of concentrations of chlorobutanol recited in Applicants’ claims.

The Examiner relies on Example 9 in Grebow (col. 13), and presumably Example 3 in APC (page 4), to assert that these references taught the use of chlorobutanol at a concentration as low as 0.1 w/v%. However, these Examples present formulations having at least two different preservatives, *i.e.*, chlorobutanol at 0.1 w/v% and phenethyl alcohol at 0.2 w/v%. APC, page 4, lines 45-47; Grebow, col. 13, lines 14-15. Thus, one of skill in the art

preparing a calcitonin formulation containing less than 0.5% w/v%, disclosed as the lowest preservative concentration for chlorobutanol in APC and Grebow, or less than 0.6% as disclosed in Azria, would have used an additional preservative. An additional preservative would have been used because as disclosed in Azria, at concentrations of 0.6% or lower, chlorobutanol was ineffective as a preservative.

The concentrations of both preservatives, in the Example cited by the Examiner, were therefore lower than the otherwise presented ranges for these two preservatives in APC and Grebow. In other words, considered in their entireties, these references suggested that one needed less of any one preservative if the formulation also included a second preservative. Thus, those skilled in the art would not have read either APC or Grebow as teaching 0.1 w/v%—or any concentration of below 0.5% for that matter—of chlorobutanol in a calcitonin formulation, when the formulation had chlorobutanol as the only listed preservative.

Applicants' pending claims recite "consisting of." Thus, the recited compositions do not include a second preservative, *i.e.*, phenethyl alcohol, the second preservative present in Example 3 of APC and Example 9 of Grebow. Those Examples would not have taught or suggested making a calcitonin formulation having 0.1% w/v chlorobutanol and lacking phenethyl alcohol. Rather, one reading these Examples would have been motivated to include another preservative, such as phenethyl alcohol, if using chlorobutanol at a concentration less than the taught range of 0.5 – 1.0% w/v.

The Examiner takes the position that because "chlorobutanol is taught to be used in combination with calcitonin, and the fact that the prior art has other ingredients besides those instantly claimed does not make the combination of calcitonin with chlorobutanol unobvious." Office Action at 9. However, the compositions of the present claims recite more than the combination of calcitonin and chlorobutanol. The claims recite a specific range of concentrations of chlorobutanol, between 0.25% and about 0.4% w/w. Thus, the combination of calcitonin with chlorobutanol is not sufficient to render the present claims obvious.

Moreover, the Examiner states "[t]he fact that the APC reference and Grebow teach other preservative[s] is also not a consideration for the use of chlorobutanol as Grebow presents a specific example that has chlorobutanol as the ingredient for a preservative,

regardless of the fact it had other ingredients in the composition.” Office Action at 9. However, the issue here is not that there were “other ingredients” in the compositions of APC and Grebow, that the Examiner relies upon in the present rejection, but that the cited composition in APC and Grebow contained an additional preservative. When read in their entirety, both references disclose the specific concentrations of chlorobutanol in particular, 0.5 – 1.0 w/v%, *i.e.*, higher than the range of concentrations of chlorobutanol recited in Applicants’ claims, but when used in conjunction with another preservative, a lower concentration of chlorobutanol may be used. Thus, the specific example the Examiner relies upon does not render obvious claims to compositions with chlorobutanol as the only preservative at a concentration of between 0.25% and about 0.4% weight/weight.

It is well established that hindsight reasoning is impermissible to support an obviousness rejection:

It is impermissible within the framework of section 103 to pick and choose from one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art.

*In re Hedges*, 228 USPQ 685, 687 (Fed. Cir. 1986). Indeed, the Examiner, in making his rejection, has used impermissible hindsight to selectively pick individual elements from the cited references to assert an alleged case of *prima facie* obviousness. To suggest now that one of ordinary skill in the art would arrive at the specific compositions claimed after reviewing the totality of the disclosures in Azria, APC and Grebow is a result of hindsight and not any teaching of the references themselves. Thus Applicants respectfully request withdrawal of the rejection.

Applicants believe that the present application is now in condition for allowance.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the

credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date March 25, 2010

FOLEY & LARDNER LLP  
Customer Number: 22428  
Telephone: (202) 295-4792  
Facsimile: (202) 672-5399

By Jacqueline D. Wright Bonilla

Jacqueline D. Wright Bonilla  
Attorney for Applicant  
Registration No. 45,239